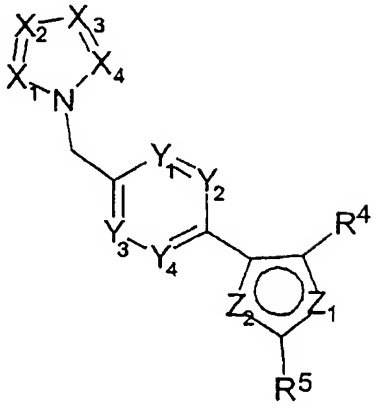
Claims

1. A compound of formula I,



I

wherein

one of X_1 and X_2 represents –N- and the other represents $-C(R^1)-$;

X_3 represents –N- or $-C(R^2)-$;

X_4 represents –N- or $-C(R^3)-$;

R^1, R^2 and R^3 independently represent H, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl or halo;

provided that, when X_1 represents $-C(R^1)-$, X_3 represents $-C(R^2)-$ and X_4 represents $-C(R^3)-$, then R^1 represents H;

Y_1, Y_2, Y_3 and Y_4 independently represent –CH- or -CF-;

Z_1 represents –CH-, -O-, -S-, -N- or -CH=CH-;

Z_2 represents –CH-, -O-, -S- or –N-;

provided that:

(a) Z_1 and Z_2 are not the same;

(b) when Z_1 represents –CH=CH-, then Z_2 may only represent –CH- or –N-; and

(c) other than in the specific case in which Z_1 represents –CH=CH-, and Z_2 represents –CH-, when one Z_1 and Z_2 represents –CH-, then the other represents –O- or –S-;

R^4 represents $-S(O)_2N(H)C(O)R^6$, $-S(O)_2N(H)S(O)_2R^6$, $-C(O)N(H)S(O)_2R^6$, or, when Z_1 represents –CH=CH-, R^4 may represent $-N(H)S(O)_2N(H)C(O)R^7$ or $-N(H)C(O)N(H)S(O)_2R^7$;

R^5 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl or di-C_{1-3}-alkylamino-C_{1-4}-alkyl;

R^6 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-3} alkoxy-C_{1-6}-alkoxy, C_{1-6} alkylamino or di-C_{1-6} alkylamino; and

R^7 represents C_{1-6} alkyl,

or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein, when X_1 represents –$C(R^1)$-, then X_3 represents –$C(R^2)$- and X_4 represents –N-.

3. A compound as claimed in Claim 2 wherein R^1 represents H.

4. A compound as claimed in Claim 1 wherein, when X_1 represents –$C(R^1)$-, then X_3 and X_4 both represent N.

5. A compound as claimed in Claim 1 wherein, when X_1 represents –$C(R^1)$-, then X_3 represents -$C(R^2)$- and X_4 represents –$C(R^3)$-.

6. A compound as claimed in Claim 1, wherein, when X_1 represents –N-, then X_3 represents –N-.

7. A compound as claimed in Claim 6 wherein, when X_4 represents –$C(R^3)$-, then R^3 represents H.

8. A compound as claimed in Claim 1, wherein, when X_1 represents –N-, then X_3 represents $-C(R^2)$ and X_4 represents $-C(R^3)$-.

9. A compound as claimed in Claim 1, wherein R^1 represents H, C_{1-3} alkyl or CF_3.

10. A compound as claimed in Claim 9, wherein R^1 represent H or ethyl.

11. A compound as claimed in Claim 1 wherein R^2 represents C_{1-3} alkyl, halo or H.

12. A compound as claimed in Claim 11 wherein R^2 represents H or methyl.

13. A compound as claimed in Claim 11 wherein R^2 represents H.

14. A compound as claimed in Claim 1 wherein R^3 represents C_{1-3} alkyl, halo or H.

15. A compound as claimed in Claim 14 wherein R^3 represents H.

16. A compound as claimed in Claim 1 wherein Y_1, Y_2, Y_3 and Y_4 all represent –CH-.

17. A compound as claimed in Claim 1 wherein Z_1 represents -S- or –CH=CH-.

18. A compound as claimed in Claim 17 wherein Z_1 represents -S-.

19. A compound as claimed in Claim 1 wherein Z_2 represents –CH-.

20. A compound as claimed in Claim 1 wherein R^4 represents $-S(O)_2N(H)C(O)R^6$.

21. A compound as claimed in Claim 1 wherein R^5 represents *n*-butyl or *iso*-butyl.

22. A compound as claimed in Claim 21 wherein R^5 represents *iso*-butyl.

23. A compound as claimed in Claim 1 wherein, when R^4 represents $-S(O)_2N(H)C(O)R^6$, $-S(O)_2N(H)S(O)_2R^6$ or $-C(O)N(H)S(O)_2R^6$, R^6 represents *n*-butoxymethyl, *iso*-butoxy or *n*-butoxy.

24. A compound as claimed in Claim 23 wherein R^6 represents *n*-butoxy.

25. A compound as claimed in Claim 1 wherein, when X_1, X_3 and X_4 all represent –CH-, Y_1, Y_2, Y_3 and Y_4 all represent –CH-, Z_1 represents –S- or –CH=CH-, Z_2 represents –CH- and R^5 represents *n*-butyl or *iso*-butyl, then R^4 represents $-S(O)_2N(H)C(O)R^6$, in which R^6 represents -O-*n*-butyl, -O-*iso*-propyl, -O-*iso*-butyl or $-CH_2$-O-*n*-butyl.

26. A compound as claimed in Claim 1, which is:
N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;
N-*iso*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;
N-*iso*-propyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;
N-(butoxyacetyl)-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-*iso*-butylbenzene-sulfonamide;

N-butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide;

N-butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide;

N-butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;

N-(butylamino)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;

N-butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;

N-butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-carboxamide;

N-butyloxycarbonyl-4-butyl-2-(4-imidazol-1-ylmethylphenyl)benzene-sulfonamide;

N-(2-methoxyethyloxy)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;

N-ethyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;

N-*tert*-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(4-methylimidazol-1-ylmethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-(4-pyrazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide;

N-butyloxycarbonyl-3-[4-(3-trifluoromethylpyrazol-1-ylmethyl)phenyl]-5-*iso*-butylthiophene-2-sulfonamide;

N-(*N*-butyl-*N*-methylamino)carbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-sulfonamide; or

N-butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-(2-methoxyethyl)-thiophene-2-sulfonamide.

27. A pharmaceutical formulation including a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

28. A method of treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

29. The method as claimed in Claim 28, wherein the condition is of the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system, or the central nervous system.

30. The method as claimed in Claim 28, wherein the condition is oesophagitis, Barrett's oesophagus, a gastric ulcer, a duodenal ulcer, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, hepatic disorders (including hepatitis), gall bladder disease, multiple organ failure, sepsis, xerostomia, gastritis, gastroparesis, hyperacidity, a disorder of the bilary tract, coelicia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion, Sjögren's syndrome, inflammatory disorders, asthma, an obstructive lung disease (including chronic obstructive lung disease), pneumonitis, pulmonary

hypertension, adult respiratory distress syndrome, renal failure, nephritis, renal hypertension, diabetic retinopathy, premature retinopathy, retinal microvascularisation, ovulatory dysfunction, hypertension, cardiac hypertrophy, cardiac failure, artherosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post baloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, angina, cardiac arrhythmias, claudicatio intermittens, preeclampsia, myocardial infarction, reinfarction, ischaemic lesions, erectile dysfunction, neointima proliferation, cognitive dysfunctions, dysfunctions of food intake (hunger/satiety), thirst, stroke, cerebral bleeding, cerebral embolus, cerebral infarction, hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, an ulcer, adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer, apoptosis, tumours, hypertrophy diabetes, neuronal lesions or organ rejection.

31. The method as claimed in Claim 28, wherein the condition is non-ulcer dyspepsia, irritable bowel syndrome, multiple organ failure, hypertension or cardiac failure.

32. A pharmaceutical formulation including a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

33. A kit of parts comprising components:

(a) a pharmaceutical formulation including a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

34. A pharmaceutical formulation including a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, and an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

35. A kit of parts comprising components:

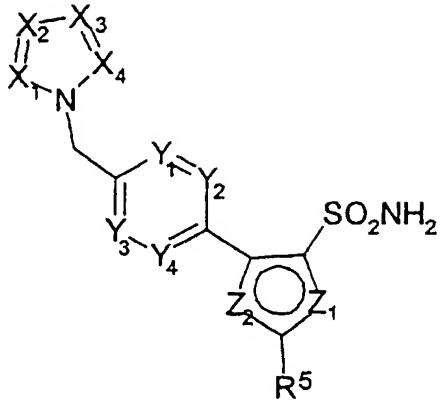
(a) a pharmaceutical formulation including a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an angiotensin converting enzyme inhibitor, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

36. A process for the preparation of a compound as defined in Claim 1, which comprises:

(i) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ or $-S(O)_2N(H)S(O)_2R^6$, and R^6 is as defined in Claim 1, reaction of a compound of formula II,



II

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1 with a compound of formula III,

$$R^6GL^1 \qquad \text{III}$$

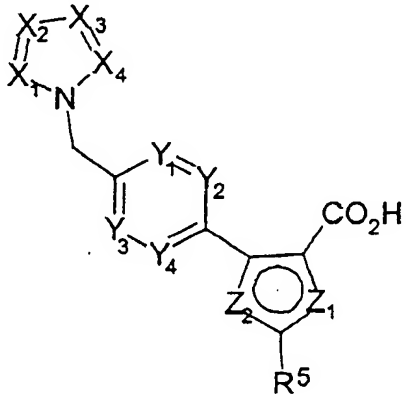
wherein G represents C(O) or $S(O)_2$ (as appropriate), L^1 represents a suitable leaving group and R^6 is as defined in Claim 1;

(ii) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkoxy-C_{1-6}-alkyl, coupling of a compound of formula II as defined above with a compound of formula IV,

$$R^{6a}CO_2H \qquad \text{IV}$$

wherein R^{6a} represents C_{1-6} alkoxy-C_{1-6}-alkyl;

(iii) for compounds of formula I in which R^4 represents $-C(O)N(H)S(O)_2R^6$ and R^6 is as defined in Claim 1, coupling of a compound of formula V,



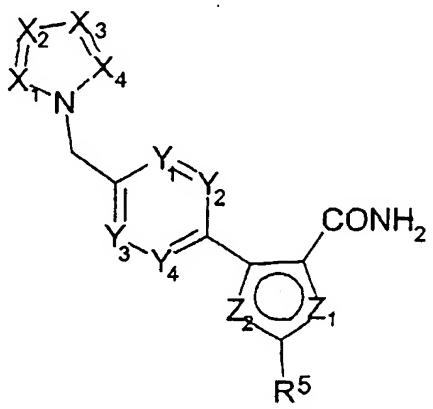
V

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1, with a compound of formula VI,

$$R^6S(O)_2NH_2 \qquad \text{VI}$$

wherein R^6 is as defined in Claim 1;

(iv) for compounds of formula I in which R^4 represents $-C(O)N(H)S(O)_2R^6$ and R^6 is as defined in Claim 1, coupling of a compound of formula VII,



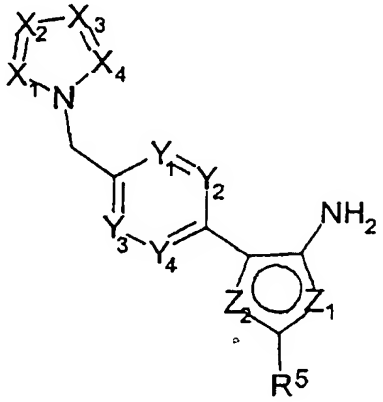
VII

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1, with a compound of formula VIII,

$$R^6S(O)_2Cl \qquad \text{VIII}$$

wherein R^6 is as defined in Claim 1;

(v) for compounds of formula I in which R^4 represents $-N(H)S(O)_2N(H)C(O)R^7$ and R^7 is as defined in Claim 1, reaction of a compound of formula IX,



IX

wherein X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, Y_4, Z_1, Z_2 and R^5 are as defined in Claim 1, with a compound of formula X,

$$R^7C(O)N(H)S(O)_2Cl \qquad \text{X}$$

wherein R^7 is as defined in Claim 1;

(vi) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as defined in Claim 1, reaction of a compound of formula IX as defined above with a compound of formula XI,

$$R^7S(O)_2N(H)C(O)OR^x \qquad XI$$

wherein R^x represents C_{1-2} alkyl and R^7 is as defined in Claim 1;

(vii) for compounds of formula I in which R^4 represents $-N(H)C(O)N(H)S(O)_2R^7$ and R^7 is as defined in Claim 1, reaction of a compound of formula IX as defined above with a compound of formula XII,

$$R^7S(O)_2NCO \qquad XII$$

wherein R^7 is as defined in Claim 1;

(viii) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkylamino, reaction of a compound of formula II as defined above with a compound of formula XIII,

$$R^{6b}NCO \qquad XIII$$

wherein R^{6b} represents C_{1-6} alkyl; or

(ix) for compounds of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents di-C_{1-6} alkylamino, reaction of a corresponding compound of formula I in which R^4 represents $-S(O)_2N(H)C(O)R^6$ and R^6 represents C_{1-6} alkoxy with a compound formula XIV,

$$R^{6c}N(H)R^{6d} \qquad XIV$$

wherein R^{6c} and R^{6d} independently represent C_{1-6} alkyl.

37. A compound of formula II as defined in Claim 36 or a protected derivative thereof.

38. A compound of formula II as claimed in Claim 36, or a protected derivative thereof, wherein X_1, X_3 and X_4 all represent –CH-, Y_1, Y_2, Y_3 and Y_4 all represent –CH-, Z_1 represents –S- or –CH=CH-, Z_2 represents –CH- and R^5 represents *n*-butyl or *iso*-butyl.

39. A compound of formula V as defined in Claim 36 or a protected derivative thereof.

40. A compound of formula VII as defined in Claim 36 or a protected derivative thereof.

41. A compound of formula IX as defined in Claim 36 or a protected derivative thereof.